

## AMENDMENTS TO THE CLAIMS

1-37. (Canceled)

38. (Currently amended) A method of inhibiting cartilage degradation in a joint of a patient, comprising: delivering to the joint a composition in solution comprising a therapeutically effective amount of a first chondroprotective agent and a therapeutically effective amount of a second chondroprotective agent, wherein the first chondroprotective agent is an anabolic chondroprotective agent that directly promotes cartilage anabolic processes and the second chondroprotective agent is an inhibitor of cartilage catabolism, and the solution is delivered locally to the joint;

wherein the anabolic chondroprotective agent is selected from the group consisting of members of the transforming growth factor- $\beta$  superfamily, including TGF- $\beta$  agonists and bone morphogenic protein agonists, that promote cartilage anabolic processes, and insulin-like growth factors that promote cartilage anabolic processes; and

wherein the inhibitor of cartilage catabolism is selected from the group consisting of IL-1 receptor antagonists that inhibit cartilage catabolism, cyclooxygenase-2 specific inhibitors that inhibit cartilage catabolism, MAP kinase inhibitors that inhibit cartilage catabolism, and nitric oxide synthase inhibitors that inhibit cartilage catabolism.

39. (Previously presented) The method of Claim 38, wherein the solution is delivered to the joint by intra-articular injection.

40. (Withdrawn) The method of Claim 39, wherein the solution comprises a sustained release delivery vehicle.

41. (Withdrawn) The method of Claim 40, wherein the sustained release delivery vehicle is selected from the group consisting of microparticles, microspheres, nanoparticles, proteins, liposomes, carbohydrates, synthetic organic compounds and inorganic compounds.

42. (Withdrawn) The method of Claim 38, wherein the solution is delivered to the joint by infusion.

43. (Withdrawn) The method of Claim 42, wherein the solution is delivered to the joint by a regulated pump delivery system.

44. (Previously presented) The method of Claim 38, wherein the solution is delivered to the joint for the treatment of a chronic cartilage degenerative condition.

45. (Previously presented) The method of Claim 38, wherein the solution is delivered to the joint prior to anticipated tissue trauma at the joint.

46. (Previously presented) The method of Claim 38, wherein the solution is delivered to the joint at or closely following a time of injury to the joint.

47. (Previously presented) The method of Claim 38, wherein the solution is delivered to the joint within a sub-acute phase following trauma to the joint.

48. (Previously presented) The method of Claim 38, wherein the solution is delivered to the joint within a chronic phase following trauma to the joint.

49. (Previously presented) The method of Claim 38, wherein the solution is locally applied prophylactically to the joint of a patient.

50. (Previously presented) The method of Claim 38, further comprising the step of identifying a patient at risk of cartilage degradation at a joint, followed by delivering the solution to the joint of the identified patient.

51. (Previously presented) The method of Claim 38, wherein each of the agents in the solution is included at a concentration or dosage that is sufficient to provide a level of inhibitory or therapeutic effect at the wound when delivered locally to the wound and that results in a plasma concentration that is less than a plasma concentration that would be required to achieve the same level of inhibitory or therapeutic effect at the wound when delivered systemically.

52. (Canceled)

53. (Previously presented) The method of Claim 38, wherein the anabolic chondroprotective agent is selected from the group consisting of TGF $\beta$ 1, TGF $\beta$ 2, TGF $\beta$ 3, BMP-2, BMP-4, BMP-6, BMP-7, and IGF-1.

54-55. (Canceled)

56. (Withdrawn) The method of Claim 38, wherein the inhibitor of cartilage catabolism comprises a soluble receptor that inhibits cartilage catabolism.

57. (Withdrawn) The method of Claim 56, wherein the soluble receptor is a soluble interleukin-1 receptor.

58. (Withdrawn) The method of Claim 56, wherein the soluble receptor is a recombinant soluble human IL-1 receptor.

59. (Withdrawn) The method of Claim 38, wherein the solution further comprises one or more pain or inflammation inhibitory agents.

60. (Withdrawn) The method of Claim 59, wherein the pain or inflammation inhibitory agents are selected from the group consisting of serotonin receptor antagonists, serotonin receptor agonists, histamine receptor antagonists, bradykinin receptor antagonists, kallikrein inhibitors, tachykinin receptor antagonists, calcitonin gene-related peptide (CGRP) receptor antagonists, interleukin receptor antagonists, inhibitors of enzymes active in the synthetic pathway for arachidonic acid metabolites, prostanoid receptor antagonists, leukotriene receptor antagonists, opioid receptor agonists, purinoceptor agonists and antagonists, adenosine triphosphate (ATP)-sensitive potassium channel openers, and calcium channel antagonists.

61-72. (Canceled)

73. (Currently amended) A method of inhibiting cartilage degradation in a joint of a patient, comprising:

delivering to the joint a composition in solution comprising a therapeutically effective amount of a first chondroprotective agent and a therapeutically effective amount of a second chondroprotective agent, wherein the first chondroprotective agent is an anabolic chondroprotective agent that directly promotes cartilage anabolic processes and the second chondroprotective agent is an inhibitor of cartilage catabolism, and the solution is delivered locally to the joint, and the solution is delivered to the joint within an acute phase following trauma to the joint;

wherein the anabolic chondroprotective agent is selected from the group consisting of members of the transforming growth factor- $\beta$  superfamily, including TGF- $\beta$  agonists and bone morphogenic protein agonists, that promote cartilage anabolic processes, and insulin-like growth

factors that promote cartilage anabolic processes and fibroblast growth factors that promote cartilage anabolic processes; and

wherein the inhibitor of cartilage catabolism is selected from the group consisting of IL-1 receptor antagonists that inhibit cartilage catabolism, cyclooxygenase-2 specific inhibitors that inhibit cartilage catabolism, MAP kinase inhibitors that inhibit cartilage catabolism, and nitric oxide synthase inhibitors that inhibit cartilage catabolism.

74. (Previously presented) The method of Claim 73, wherein the solution is delivered during an acute phase following surgery.

75. (Previously presented) The method of Claim 73, wherein the solution is delivered to the joint within a four week period following trauma to the joint.

76. (Previously presented) The method of Claim 73, wherein the solution is delivered to the joint by intra-articular injection.

77. (Withdrawn) The method of Claim 73, wherein the solution comprises a sustained release delivery vehicle.

78. (Withdrawn) The method of Claim 77, wherein the sustained release delivery vehicle is selected from the group consisting of microparticles, microspheres, nanoparticles, proteins, liposomes, carbohydrates, synthetic organic compounds and inorganic compounds.

79. (Withdrawn) The method of Claim 73, wherein the solution is delivered to the joint by infusion.

80. (Withdrawn) The method of Claim 79, wherein the solution is delivered to the joint by a regulated pump delivery system.

81. (Previously presented) The method of Claim 73, wherein each of the agents in the solution is included at a concentration or dosage that is sufficient to provide a level of inhibitory or therapeutic effect at the wound when delivered locally to the wound and that results in a plasma concentration that is less than a plasma concentration that would be required to achieve the same level of inhibitory or therapeutic effect at the wound when delivered systemically.

82. (Previously presented) The method of Claim 38, wherein the composition comprises a combination of an anabolic chondroprotective agent and an inhibitor of cartilage catabolism, the combination selected from the group consisting of: an insulin-like growth factor that promotes cartilage anabolic processes and a nitric oxide synthase inhibitor that inhibits cartilage catabolism; a member of the transforming growth factor- $\beta$  superfamily and a cyclooxygenase-2 specific inhibitor that inhibits cartilage catabolism; a member of the transforming growth factor- $\beta$  superfamily and a MAP kinase inhibitor that inhibits cartilage catabolism; and an insulin-like growth factor that promotes cartilage anabolic processes and an IL-1 receptor antagonist that inhibits cartilage catabolism.

83. (Previously presented) The method of Claim 73, wherein the composition comprises a combination of an anabolic chondroprotective agent and an inhibitor of cartilage catabolism, the combination selected from the group consisting of: an insulin-like growth factor that promotes cartilage anabolic processes and a nitric oxide synthase inhibitor that inhibits cartilage catabolism; a member of the transforming growth factor- $\beta$  superfamily and a cyclooxygenase-2 specific inhibitor that inhibits cartilage catabolism; a member of the transforming growth factor- $\beta$  superfamily and a MAP kinase inhibitor that inhibits cartilage

catabolism; and an insulin-like growth factor that promotes cartilage anabolic processes and an IL-1 receptor antagonist that inhibits cartilage catabolism.

LAW OFFICES OF  
CHRISTENSEN O'CONNOR JOHNSON KINDNESS<sup>PLLC</sup>  
1420 Fifth Avenue  
Suite 2800  
Seattle, Washington 98101  
206.682.8100